UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,183	01/23/2001	Jeno Gyuris	GPCI-P03-109	1943

28120 7590 04/02/2002

ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
DAVIS, NATALIE A

ART UNIT	PAPER NUMBER
1642	8

DATE MAILED: 04/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,183	GYURIS ET AL.	
	Examiner	Art Unit	
	Natalie A. Davis	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *1-27,34-53 and 88-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33 and 54-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-27, 34, and 49-53, drawn to a chimeric polypeptide, classified in class 530, subclass 363.

II. Claims 28-33, drawn to a nucleic acid, classified in class 536, subclass 23.1.

III. Claim 35 and 47, drawn to a method of treating a disease using a chimeric polypeptide, classified in class 514, subclass 2.

IV. Claims 36, 38, and 48, drawn to a method of disease *in vivo* using genetic material, classified in class 514, subclass 44.

V. Claims 37-38, drawn to a method of treating a disease *ex vivo* using genetic material, classified in class 514, subclass 44.

VI. Claims 39-42, drawn to a chimeric polypeptide having $(A\text{-}B\text{-}C)_n$ structure, classified in class 530, subclass 387.3.

VII. Claims 43-46, drawn to a chimeric polypeptide comprising serum albumin having at least two biologically active heterologous peptide sequences, classified in class 530, subclass 387.3.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I-II and VI-VII (products) and III-V (methods) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the products of Groups I-II and VI-VII may be used for a number of different processes that are very much unrelated. For example, the polypeptide of Groups I, VI-VII may not only be used in the method of Group III, but may also be used for affinity purification. Likewise, the nucleic acid of Group II may be used for making a protein or used as a probe and not just in the methods of Groups IV-V.

3. The products of I-II and VI-VII are drawn to structurally and functionally different molecules with different immunological properties, each invention requires different reagents and steps to make and characterize it.

4. The methods of Groups III-V relate to methods but each method differs in method steps, modes of operation, reagents needed and serve different endpoints and effects. For example, even though the methods of both Groups III and IV are drawn towards treatment, the method steps and mode of action will be different as one is practiced *in vivo* and the other is practiced *ex vivo.*

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, divergent subject matter, and require different search strategies, restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. During a telephone conversation with Mathew Vincent on 2 January 2002, a election requirement was made as indicated above. A voicemail message was received from Yu Lu on 2 January 2002, wherein a provisional election was made to prosecute the invention of Group II, claims 28-33. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-27, 34-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. Applicant's traversal of the election of Group II, claims 28-33 is acknowledged. The traversal is on the ground(s) that the inventions of Groups III-V only have 6 claims and may be examined without a serious burden because they are directed to methods of using the products of Groups I and II. This is not found persuasive for reasons indicated in the previous office action, as the Groups have different class/subclass, thus rendering them independent and distinct and a serious burden to search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 28-33 are being examined as belonging to the elected Group II, while claims 1-27, 34-53 are withdrawn from examination as being drawn to a non-elected invention.

8. Applicant's amendment filed 9 January 2002 (Paper No: 7) is acknowledged. Accordingly, claims 28-29, 31, and 33 are amended, and claims 54-92 are new. Claims 28-33 and 54-88 are under examination. Claims 88-92 are withdrawn from examination as being drawn to a non-elected invention due to structural differences.

Information Disclosure Statement

9. The information disclosure statement has been considered. A signed copy is attached hereto.

Specification

10. The disclosure is objected to because of the following informality: The specification makes reference to amino acid sequences on pages 4, and 38 and 40. All nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids, provided that there are at least 4 "specifically defined" nucleotides or amino acids embedded within the text of the disclosure must be referenced by sequence identifiers (SEQ ID NO:). The rules apply to all sequences in a given application, whether claimed or not. Correction is required. See MPEP § 2422.03.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 86 and 88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 86 and 88 are indefinite in the recitation of the phrase "Cys 53-Cys 62...". The claim is indefinite because there is no frame of reference in the claim or the specification supplied that will uniquely identify the amino acids of position 53-62 of the cysteine loop.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-33, and 54-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

13. The specification does not indicate what biological activity the heterologous peptide that is encoded by the nucleic acid must possess. Accordingly, one of ordinary skill in the art would not know how to make and use the invention because one would not know how to assay and select for the polypeptide since the biological activity of the heterologous peptide has not been defined.

14. The nature of the invention is to a nucleic acid encoding a chimeric polypeptide comprising serum albumin with biologically active heterologous peptide inserted within, wherein the chimeric polypeptide exhibits increased biological activity as compared to the heterologous peptide alone, wherein the sequence shares less than 40% identity with a sequence to which it is compared (p. 10). Claims 54-56 are drawn to a nucleic acids encoding chimeric polypeptides which, comprise fragments of serum albumin or anigiogensis-inhibiting polypeptides. There are many heterologous polypeptide molecules, which have less than 40% identity with a sequence to

which it is compared and many fragments of serum albumin or anigiogensis-inhibiting polypeptides that may or may not perform the same biological functions and the specification does not give any guidance to which molecules will exhibit the biological activities as the claimed, or any guidance as to which regions of amino acid sequence are responsible for biological activity and thus, must be preserved so the molecule will function as claimed. Thus, it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences, which are capable of functioning as contemplated. One cannot extrapolate the teachings of the specification to the breadth of the claims because the claims are broadly drawn to any nucleic acids encoding a chimeric polypeptide comprising a heterologous polypeptide and fragments of serum albumin or anigiogensis-inhibiting polypeptides and applicant has not enabled all of these types of modifications because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed. Reasonable correlation must exist between the breadth of the claims and the enablement set forth, and it cannot be predicted from the disclosure as to which polypeptides and fragments should be isolated.

15. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative

substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Therefore, in view of the unpredictability in the art, lack of working examples, the breadth of the claims, and insufficient guidance as indicated above, one of skill in the art would not be able to practice the claimed invention because undue experimentation would be required.

16. Claims 28-33, and 54-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar (CA FC) 19 USPQ2d 1111 (6/7/1991) clearly states that "written description" of invention required by first paragraph of 35 U.S.C. 112 is separate and distinct from that paragraph's requirement of enabling disclosure, since description must do more than merely provide explanation of how to "make and use" invention; applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed. An applicant shows possession by describing the claimed invention with all it limitations using such descriptive means as words, structures, diagrams, and formulas. Also, description of an actual reduction to practice, or by showing the invention was "ready for patenting," or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention at the time of filing.

17. The elected claims are drawn to a nucleic acid that encodes a chimeric polypeptide comprising a heterologous polypeptide and may comprise fragments of serum albumin or anigiogensis-inhibiting polypeptides, such as angiostatin and endostatin. The specification does not disclose any objective evidence regarding the isolation of and assaying of the claimed nucleic acid, the successful binding of a heterologous polypeptide to a tyrosine kinase receptor, the induction of apoptosis, modulation of cell proliferation or differentiation of cell types. Likewise, there is no evidence of the chimeric polypeptide encoded by the nucleic acid exhibiting a half-life of no less than 14 or 10 days in the blood. In addition, no other examples are disclosed that

conveys to one of skill in the art that the applicant was in possession of the claimed nucleic acid. There is no actual reduction to practice, sufficient descriptive information, such as definitive structural features, which are critical to activity, or complete detailed description of the function of claimed invention indicating that the claimed nucleic acid or fragments were indeed isolated, produced, and assayed for the uses disclosed. Thus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa PhD can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis, PhD
March 25, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600